CLAIMS

What is claimed is:

1. A method for generating a library of chimeric polynucleotides, comprising:

a) aligning the sequences of a basis set of polynucleotides, wherein the basis set comprises three or more different polynucleotides;

b) identifying areas of homology between each polynucleotide in the basis set and at least one other polynucleotide in the basis;

c) identifying splice points in each polynucleotide in the basis set which correspond to areas of homology identified in step (b);

d) preparing a set of oligonucleotide double primers, wherein each double primer comprises a "pre" region joined to and followed immediately by a "post" region, and wherein the "pre" region comprises an oligonucleotide primer for a splice point in one polynucleotide identified in the basis set, and the "post" region comprises the complement of an oligonucleotide primer for the corresponding splice point in another polynucleotide in the basis set, and wherein two or three of the following are satisfied: (i) the set of double primers includes double primers comprising exact matches or near matches for all possible combinations of pre and post regions for each splice point; (ii) at least one double primer is capable of priming more than one polynucleotide in the basis set in the pre and/or post regions; and (iii) the set includes at least one double primer that does not prime at least one polynucleotide in the basis set;

e) hybridizing under hybridization conditions said double primers to said basis set or fragments thereof comprising said splice points, thereby generating hybridized complexes;

f) amplifying in a polymerase chain reaction the hybridized complexes of step (e), thereby generating a library of chimeric polynucleotides,

wherein each chimeric polynucleotide comprises a fragment from at least two of the polynucleotides in the basis set and fragments of each polynucleotide are incorporated into the library.

2. The method of Claim 1 wherein at least two of the polynucleotides of the basis set have high homology to one another.

3. The method of Claim 1 wherein at least two of the polynucleotides of the basis set have low homology to one another.

4. The method of Claim 1, wherein the basis set comprises at least a first polynucleotide, a second polynucleotide and a third polynucleotide; said first and second polynucleotides have at least one area of high homology corresponding to a first splice point in said first and second polynucleotides thereby identifying a first splice point for priming a first double primer; and said third polynucleotide has an area of low homology with said first polynucleotide which corresponds to said first splice point whereby said first double primer does not prime said third polynucleotide under the conditions of steps (e) and (f).

5. The method of Claim 4 further comprising the step of identifying an area of high homology between said first and third polynucleotides in an area adjacent to said first splice point, thereby identifying a second splice point for priming a second double primer between said first and third polynucleotides.

6. The method of Claim 5 wherein the number of splice points in said first polynucleotide is greater than the number of splice points in said second and/or third polynucleotides.

7. The method of Claim 5 further comprising the step of identifying an area of high homology between said second and third polynucleotides in an area adjacent to said first splice point, thereby identifying a third splice point for priming a third double primer between said second and third polynucleotides.

8. The method of Claim 5 wherein the "pre" region of at least one double primer hybridizes to at least two polynucleotides.

9. The method of Claim 8 wherein the "post" region of at least one double primer hybridizes to at least two polynucleotides.

10. The method of Claim 1 at least one of the polynucleotides of the basis set comprises the entire coding sequence of a gene.

11. The method of Claim 1 wherein at least one of the polynucleotides of the basis set comprises a synthetic nucleic acid.

12. The method of Claim 1 wherein steps (a)-(c) are executed by use of an algorithm.

13. The method of Claim 12, wherein the algorithm is executed by a computer processing unit.

14. The method of Claim 13, wherein the algorithm requires input of a minimum distance between splice points and/or number of double primers per polynucleotide.

15. The method of Claim 13, wherein the algorithm incorporates weighing factors to bias selection of splice points.

16. The method of Claim 15, wherein the weighing factors bias selection of splice points between regions of interest in the polynucleotides of the basis set.

17. The method of Claim 16, wherein the weighing factors bias selection of splice points in regions having a percentage of identity of at least about 90% between at least two of said polynucleotides in the basis set.

18. The method of Claim 16, wherein the weighing factors bias selection of splice points between structurally identifiable regions of the polypeptides encoded by the polynucleotides of the basis set.

19. The method of Claim 1 further comprising a step of contacting a chip characterized by a set of primers which hybridize to one or more of the terminal sequences of the polynucleotides in the basis set with the basis set, whereby the library of chimeric polynucleotides is generated on said chip.

21. The method of Claim 1 further comprising contacting said polynucleotides of said basis set with one or more blocking oligonucleotides having high homology with at least one region of at least one of said polynucleotides, whereby each of said oligonucleotides hybridizes to said polynucleotide and interrupts the polymerase chain reaction of step (f).

22. The method of Claim 21, wherein said blocking oligonucleotides are characterized by a covalent modification of the 3' end.

23. The method of Claim 21, wherein said blocking oligonucleotides are each characterized by a non-complementary base at the 3' end.

24. A method for generating a library of chimeric polynucleotides, comprising:

a) aligning the sequences of a basis set of polynucleotides, wherein the basis set comprises two or more different polynucleotides;

b) identifying areas of homology between each polynucleotide in the basis set;

c) identifying splice points in each polynucleotide in the basis set which correspond to areas of homology identified in step (b);

d) preparing a set of oligonucleotide double primers, wherein each double primer comprises a "pre" region joined to and followed immediately by a "post" region, and wherein the "pre" region comprises an oligonucleotide primer for a splice point in one polynucleotide identified in the basis set, and the "post" region comprises the complement of an oligonucleotide primer for the corresponding splice point in another polynucleotide in the basis set, and wherein the set of double primers includes double primers comprising all possible combinations of pre and post regions for each splice point;

e) preparing a set of blocking oligonucleotides that hybridize to regions of the basis polynucleotides;

f) hybridizing under hybridization conditions said double primers and blocking oligonucleotides to said basis set or fragments thereof comprising said splice points, thereby generating hybridized complexes;

g) amplifying in a polymerase chain reaction the hybridized complexes of step (e) under non strand displacing conditions, whereby the blocking oligonucleotides interrupt the reaction thereby generating a library of chimeric polynucleotides,

wherein each chimeric polynucleotide comprises a fragment from at least two of the polynucleotides in the basis set and fragments of each polynucleotide are incorporated into the library.

25. The method of Claim 24 further comprising the steps of (h) denaturing the product of step (g) and repeating steps (e) through (g), using the extension chimeric polynucleotides obtained from step (h) as primers in step (f).

26. The method of Claim 25 wherein the blocking oligonucleotides correspond to a part of a double primer sequence.

27. The method of Claim 25, wherein the algorithm requires input of at least one of the following: a minimum distance between splice points; number of double primers per polynucleotide; number of blocking oligonucleotides per polynucleotide; distance between a blocking oligonucleotide and an adjacent splice point.

28. The method of Claim 27, wherein the algorithm incorporates weighing factors to bias selection of splice points and blocking oligonucleotides.

29. The method of Claim 28, wherein the weighing factors bias selection of splice points and blocking oligonucleotides between regions of interest in the polynucleotides of the basis set.

30. The method of Claim 24, wherein said blocking oligonucleotides are characterized by a covalent modification of the 3' end.

31. The method of Claim 24, wherein said blocking oligonucleotides are each characterized by a non-complementary base at the 3' end.

32. A method for manufacturing chimeric polynucleotides, the improvement comprising the steps of (a) preparing a set of blocking oligonucleotides that hybridize to regions of the basis polynucleotides; (b) hybridizing under hybridization conditions said blocking oligonucleotides to a basis set of

polynucleotides to be chimerized, thereby generating hybridized complexes; (c) amplifying in a polymerase chain reaction the hybridized complexes of step (b), whereby the blocking oligonucleotides interrupt the reaction thereby generating a library of chimeric polynucleotides.

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